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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/782,974	02/14/2001	Peter Lind	00411.US1/PHRM-0311	5217

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EXAMINER	
MURPHY, JOSEPH F	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 05/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/782,974	LIND ET AL.	
	Examiner	Art Unit	
	Joseph F Murphy	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *4/6/2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-81* is/are pending in the application.

4a) Of the above claim(s) *1-31 and 36-81* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Formal Matters

Claims 1-81 are pending. Claims 1-29, 36-81 stand withdrawn from consideration pursuant to 37 CFR 1.142(b). Claims 30-31 were cancelled. Claims 32-35 are under consideration.

Response to Amendment and Arguments

Applicant's amendment and the arguments filed 2/2/2004 have been fully considered but they are persuasive in part, for the reasons set forth below.

The rejection of claims 32 and 33 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention has been obviated by Applicants amendment and is thus withdrawn.

Specification

The title of the invention is not descriptive. Applicant should avoid the use of novel in the title, as patents are presumed to be novel and unobvious.

Claim Rejections - 35 USC §§ 101, 112, first paragraph

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 32-35 stand rejected under 35 U.S.C. § 101 because they are drawn to an invention with no apparent or disclosed patentable utility, for reasons of record set forth in the Office Action of 7/29/2003. The instant application has provided a description of an isolated DNA encoding a protein and the protein encoded thereby. The instant application does not disclose the biological role of this protein or its significance. The claimed invention is not supported by either a credible, specific and substantial asserted utility or a well-established utility. Novel biological molecules lack well-established utility and must undergo extensive experimentation. Applicant is directed to the Utility Examination Guidelines, Federal Register, Vol. 66, No. 4, pages 1092-1099, Friday January 5, 2001.

The rejection of record set forth that it is clear from the instant specification that the nucleic acid encoding the NGPCR-14 polypeptide has been assigned a function because of its similarity to known proteins (Specification at 78, lines 4-8). However, it is commonly known in the art that sequence-to-function methods of assigning protein function are prone to errors (Doerks et al.1998). These errors can be due to sequence similarity of the query region to a region of the alleged similar protein that is not the active site, as well as homologs that did not have the same catalytic activity because active site residues of the characterized family were not conserved (Doerks et al. page 248, column 3, fourth and fifth paragraphs). Inaccurate use of sequence-to-function methods have led to significant function-annotation errors in the sequence databases (Doerks et al. page 250, column 1, third paragraph). Furthermore, Brenner (1999, Trends in Genetics 15:132-133) argues that accurate inference of function from homology must be a difficult problem since, assuming there are only about 1000 major gene superfamilies in

nature, then most homologs must have different molecular and cellular functions. Finally, Bork et al. (1996, Trends in Genetics 12:425-427) add that the software robots that assign functions to new proteins often assign a function to a whole new protein based on structural similarity of a small domain of the new protein to a small domain of a known protein. Such questionable interpretations are written into the sequence database and are then considered facts.

Additionally, even if, *arguendo*, the nucleic acid encoding the NGPCR-14 protein is found to be a G-protein coupled receptor, it is an orphan receptor. Since the ligand to this receptor is unknown, the function of the protein is also unknown. Neither the specification nor the art of record disclose any diseases or conditions associated with the function or expression of the NGPCR-14 protein, therefore, there is no "real world" context of use. Further research to identify or reasonably confirm a "real world" context of use is required. In the instant case, the fact that the claimed invention encodes a GPCR is not sufficient to establish a specific and substantial utility. Although GPCRs have been found to be involved in many different processes and have been the target of much research and drug discovery, unless the specific ligand for each receptor is known, unless the biological activity of the receptor is disclosed or unless the processes that each receptor is involved in are identified, the receptor has no "real world" use, and therefore, lacks specific and substantial utility.

After complete characterization, this protein may be found to have a patentable utility. This further characterization, however, is part of the act of invention and until it has been undertaken Applicant's claimed invention is incomplete. The instant situation is directly analogous to that which was addressed in *Brenner v. Manson,* 148 USPQ 689 (Sup. Ct., 1966), in which a novel compound which was structurally analogous to other compounds which were

known to possess anticancer activity was alleged to be potentially useful as an antitumor agent in the absence of evidence supporting this utility. The court expressed the opinion that all chemical compounds are "useful" to the chemical arts when this term is given its broadest interpretation. However, the court held that this broad interpretation was not the intended definition of "useful" as it appears in 35 USC § 101, which requires that an invention must have either an immediately obvious or fully disclosed "real world" utility. The court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

The instant claims are drawn to a nucleic acid encoding a polypeptide which has an as yet undetermined function or biological significance. Until some actual and specific significance can be attributed to the protein identified in the specification as NGPCR-14, the instant invention is incomplete. The polypeptide encoded by the nucleic acids of the instant invention is known to be structurally analogous to proteins that are known in the art as G protein coupled receptors. In the absence of knowledge of the natural substrate or biological significance of this protein, there is no immediately obvious patentable use for it. To employ a protein of the instant invention in the identification of substances which inhibit its activity is clearly to use it as the object of further research which has been determined by the courts to be a non-patentable utility. Since the instant specification does not disclose a "real world" use for NGPCR-14 then the claimed

invention is incomplete and, therefore, does not meet the requirements of 35 USC § 101 as being useful.

Claims 32-35 also stand rejected under 35 U.S.C. 112, first paragraph, for reasons of record set forth in the Office Action of 7/29/2003. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Applicant argues that under the Patent Law, the USPTO must accept the applicant's demonstration that the polypeptide encoded by the claimed invention is a member of a particular protein family and that utility is proven by a reasonable probability unless the USPTO can demonstrate through evidence or sound scientific reasoning that a person of ordinary skill in the art would doubt the asserted utility, and that the Examiner has simply not provided sufficient evidence or sound scientific reasoning to the contrary. However, the Examiner cited the Doerks reference to show that it is commonly known in the art that sequence-to-function methods of assigning protein function are prone to errors. Doerks discuses several proteins that have had their function predicted based on homology to known proteins, for example, an assignment error was made for proteins gil2314657 and gil2688341 based on significant similarity to proline dipeptidases, when this assignment was based on similarity of a region that was not the active site (page 248 column 3, third full paragraph). The Brenner reference was cited to show that accurate inference of function from homology must be a difficult problem since, assuming there are only about 1000 major gene superfamilies in nature, then most homologs must have different molecular and cellular functions. Thus, based on the teachings of Doerks, Brenner and Bork, the

determination of a function for an encoded polypeptide based on sequence data is difficult and does not provide a well-established utility for the claimed polypeptide and polynucleotide. Additionally, the Examiner cites Yan et al. which teaches that in certain cases, a change of even two-amino acid residues in a protein results in switching the binding of the protein from one receptor to another (Yan et al., Two-amino acid molecular switch in an epithelial morphogen that regulates binding to two distinct receptors. Science 290: 523-527, 2000). Thus, the asserted utilities in the specification based upon the protein sequence homology are not specific and substantial.

Applicant further argues that the allegations that there is no well established utility for proteins of the GPCR class that the Applicants are now claiming is directly refuted by industry evidence. This is not found to be persuasive. The GPCR family is functionally highly diverse, as evidenced by the Stadel reference (see page 432, Table 1). When there is great functional diversity in a structurally related class of compounds, the class cannot be used to predict a utility for a new compound that fits in the class by structural similarity. Such is the case here.

Applicants further submit several issued US Patents and allege that they are evidence of an art recognized utility for G-protein coupled receptors whose natural ligand is unknown. First, each Application is examined on its own merits. Additionally, the Examiner cites the Stadel reference, which teaches that the initial challenge is to determine the function of each orphan receptor through the identification of activating ligands and, once the function is clarified, link the orphan receptor to a specific disease and thus establish it as a candidate for a comprehensive drug discovery effort (page 433, column 1, first paragraph). Thus Stadel et al. teaches that before an orphan GPCR has a use, the activating ligand must be determined. Thus, without a

known ligand, orphan receptors do not have a well-established, specific or substantial utility. Applicants cite the Marchese reference to demonstrate that the task of identifying GPCR's is of prime importance. However, Stadel et al. teaches that characterized GPCR's are attractive therapeutic targets, and that orphan receptors may have a similar potential, but that their activating ligand must first be determined (page 433, column 1, first paragraph).

Applicant further argues that the encoded protein can be used for the identification of ligands. However, as discussed above, Stadel et al. teaches that before an orphan GPCR has a use, the activating ligand must be determined. Thus, without a known ligand, orphan receptors do not have a well-established, specific or substantial utility. This is only a research use and research uses only designed to identify a particular function of the claimed molecules and are not a substantial utility. See, e.g., Brenner v. Manson, 383 U.S. 519, 148 USPQ 689 (Sup. Ct. 1966) wherein a research utility was not considered a "substantial utility." Moreover, such uses are not specific to the instant molecule, rather applicable to any nucleic acid molecules or proteins.

The rejection of record set forth that even if, *arguendo*, the NGPCR-14 polynucleotide and polypeptides are found to have a patentable utility, claims 32-35 stand rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for a polypeptide comprising a fragment of SEQ ID NO: 192, or a polypeptide comprising an amino acid sequence homologous to SEQ ID NO: 192, or a polypeptide comprising an amino acid comprising at least one conservative amino acid substitution compared to the sequence of

SEQ ID NO: 192, for reasons of record set forth in the Office Action of 7/29/2003. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. See In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue.

The rejection of record set forth that in the instant case, the claims are directed to a polypeptide comprising a fragment of SEQ ID NO: 192, or a polypeptide comprising an amino acid sequence homologous to SEQ ID NO: 192, or a polypeptide comprising an amino acid comprising at least one conservative amino acid substitution compared to the sequence of SEQ ID NO: 192. Thus, the claims encompass variant proteins. Applicant has only taught SEQ ID NO: 192. Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active muteins, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. Applicants do not disclose any actual or

prophetic examples on expected performance parameters of any of the possible muteins of NGPCR-14.

It is known in the art that even single amino acid changes or differences in the amino acid sequence of a protein can have dramatic effects on the protein's function. For example, Voet et al. (1990) teaches that a single Glu to Val substitution in the beta subunit of hemoglobin causes the hemoglobin molecules to associate with one another in such a manner that, in homozygous individuals, erythrocytes are altered from their normal discoid shape and assume the sickle shape characteristic of sickle-cell anemia, causing hemolytic anemia and blood flow blockages (pages 126-128, section 6-3A and page 230, column 2, first paragraph). It is also known in the art that a single amino acid change in a protein's sequence can drastically affect the structure of the protein and the architecture of an entire cell. Thus, the amino acid sequence of a polypeptide determines its structural and functional properties, and predictability of which amino acids can be substituted is extremely complex and well outside the realm of routine experimentation, because accurate predictions of a polypeptide's structure from mere sequence data are limited. Since detailed information regarding the structural and functional requirements of the encoded proteins are lacking, it is unpredictable as to which encoding variations, if any, meet the limitations of the claims.

Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the

effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Given the breadth of claims 32-35 in light of the predictability of the art as determined by the number of working examples, the level of skill of the artisan, and the guidance provided in the instant specification and the prior art of record, it would require undue experimentation for one of ordinary skill in the art to practice the claimed invention.

Applicant argues that the Federal Circuit has specifically validated the proposition that a disclosure that utilizes routine screening using well know procedures to make the invention constitutes an enabling disclosure. However, Applicant is required to enable one of skill in the art to make and use the claimed invention, while the claims encompass methods using polypeptides which the specification only teaches one skilled in the art to test for functional variants to be used in the claimed method. It would require undue experimentation for one of skill in the art to make and use the claimed polynucleotides, since the skilled artisan would have to first make polynucleotides encoding polypeptide variants of NGPCR-14, then test for function. Because the amino acid sequence of a polypeptide determines its structural and functional properties, and predictability of which amino acids can be substituted is extremely complex, accurate predictions of a polypeptide's structure from mere sequence data are limited. Thus, since Applicant has only taught how to test for encoded polypeptide variants of NGPCR-14, and has not taught how to make polynucleotides encoding polypeptide variants of NGPCR-14, it would require undue experimentation of one of skill in the art to make and use the claimed polynucleotides.

Applicant cites Hybritech, and argues that the Federal Circuit has specifically validated the proposition that a disclosure that utilizes routine screening using well know procedures to make the invention constitutes an enabling disclosure. However, in Hybritech, the Court wrote that " With respect to screening, the only permissible view of the evidence is that screening methods used to identify the necessary characteristics, including affinity, of the monoclonal antibodies used in the invention were known in the art and that the '110 patent contemplated one of those". This is inapposite to the facts of the instant case. In Hybritech, as the Court states, the necessary characteristics of the antibodies to be screened were known, i.e. the affinity of the antibodies to the target protein, and contemplated in the '110 patent. Here, the Specification does not disclose a function for the claimed polypeptides, and thus the skilled artisan would need to determine the function of SEQ ID NO: 192, then make the polypeptide variants, then screen for the determined function. This would require undue experimentation.

Claims 32-35 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for reasons of record set forth in the Office Action of 7/29/2003. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

The rejection of record set forth that these are genus claims. The claims are drawn to a polypeptide comprising a fragment of SEQ ID NO: 192, or a polypeptide comprising an amino acid sequence homologous to SEQ ID NO: 192, or a polypeptide comprising an amino acid comprising at least one conservative amino acid substitution compared to the sequence of SEQ ID NO: 192. Thus, the claims encompass variant proteins. Applicant has only taught SEQ ID NO: 192. The specification and claim do not indicate what distinguishing attributes shared by the members of the genus. The specification and claim do not place any limit on the number of amino acid substitutions, deletions, insertions and/or additions that may be made to SEQ ID NO: 192. Thus, the scope of the claim includes numerous structural variants, and the genus is highly variant because a significant number of structural differences between genus members is permitted. The specification and claims do not provide any guidance as to what changes should be made. Structural features that could distinguish compounds in the genus from others in the protein class are missing from the disclosure. No common structural attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, applicant was not in possession of the claimed genus.

Applicant argues that the additional limitations overcome the WD rejection. In the instant case, the claims are drawn to polypeptide variants of NGPCR-14. The skilled artisan would not be apprised of the metes and bounds of the functional limitation with regard to

NGPCR-14 activity. The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. In the instant case, the specification fails to provide sufficient descriptive information, such as definitive structural or functional features of the genus of polypeptides used in the claimed method. There is no description of the conserved regions which are critical to the structure and function of the genus claimed. There is no description of the sites at which variability may be tolerated and there is no information regarding the relation of structure to function. Structural features that could distinguish the compounds in the genus from other seven transmembrane region compounds are missing from the disclosure. Furthermore, the prior art does not provide compensatory structural or correlative teachings sufficient to enable one of skill to isolate and identify the polypeptides encompassed: there is no guidance in the art as to what the defining characteristics of the polypeptides might be. Thus, no identifying characteristics or properties of the instant polynucleotides encoding polypeptides are provided such that one of skill would be able to predictably identify the molecules that would retain any activity of NGPCR-14 polypeptides.

Conclusion

No claim is allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Murphy whose telephone number is (571) 272-0877. The examiner can normally be reached Monday through Friday from 7:30 am to 5:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (571) 272-0887.

The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Art Unit 1646
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